Diosmin Dose and Safety

Author / Study Title	Dose Range	Treatment Duration	Number of Subjects	Safety Results
Amato, 1994 [Ref. 16] Advantage of a micronized flavonoidic fraction (Daflon 500 mg) in comparison with a non-micronized diosmin.	Micronized diosmin versus non-micronized diosmin 1000 mg/day	2 months	90 patients	Satisfactory clinical tolerance: 5 cases of epigastric pain in the non-micronized group and 7 cases in the micronized group. All these events resolved spontaneously without dose change.
Belcaro et al., 1995 [Ref. 17] Laser Doppler and transcutaneous oximetry: modern investigations to assess drug efficacy in chronic venous insufficiency.	Diosmin complex 500 mg/day (group 1) versus 1000 mg/day (group 2) versus 2000 mg/day (group 3)	3 months	104 patients	Mild adverse event occurred in one patient of group 1 (inguinal pain) and in two patients in group 3 (gastralgia and cystitis). Adverse events disappeared after treatment discontinuation.
Belcaro et al., 2002 [Ref. 26] HR (Venoruton 1000, Paroven, 0-[beta-hydroxyethyl]-rutosides) vs. Daflon 500 in chronic venous disease and microangiopathy: an independent prospective, controlled, randomized trial.	Diosmin 500 mg/day versus Venoruton 1000 mg/day	8 weeks	90 patients	No side effects due to treatment. Very good compliance and tolerability. No withdrawal from the study.
Buckshee et al., 1997 [Ref. 3] Micronized flavonoid therapy in internal hemorrhoids of pregnancy	Diosmin complex at 3 dosing levels	3 months	50 women	Good tolerance to diosmin complex. Treatment did not affect pregnancy, fetal development, birth weight, infant growth and feeding.
Cesarone et al., 1993 [Ref. 11] Capillary filtration and ankle edema in patients with venous hypertension: effects of Daflon.	Diosmin complex 1500 mg per day versus 1000 mg per day	4 weeks	53 patients	The treatments were well tolerated and no side effects were reported.
Cospite et al., 1989 [Ref. 6] Double blind study of the pharmacodynamic and clinical activities of 5682 SE in venous insufficiency. Advantages of the new micronized form.	Micronized diosmin 1000 mg/day versus non-micronized diosmin 900 mg/day	2 months	90 patients	Clinical and laboratory acceptabilities were similar in both groups. Five patients reported epigastric pain in the non-micronized group and seven in the micronized group.

Cospite, 1994 [Ref. 14] Double-blind, placebo-controlled evaluation of clinical activity and safety of Daflon 500 mg in the treatment of acute hemorrhoids.	Diosmin complex (3000 mg/day for 4 days and then 2000 mg/day for 3 days) versus placebo	7 days	100 patients	No patient withdrew because of an adverse event. Acceptability was good. Seven patients reported at least one side effect: 4 patients in the Diosmin group and 3 in the placebo group.
Danielsson et al., 2002 [Ref. 27] A randomized controlled trial of micronized purified flavonoid fraction vs. placebo in patients with chronic venous disease.	Diosmin complex 1000 mg/day versus placebo	60 days	101 patients	Mild side effects reported by 12 % of patients in the diosmin group and 4 % in the placebo group. Two patients withdrew because of side effect (nausea): 1 in the diosmin group and 1 in the placebo group.
Galley and Thiollet, 1993 [Ref. 10] A double-blind, placebo-controlled trial of a new venoactive flavonoid fraction (S 5682) in the treatment of symptomatic capillary fragility.	Diosmin complex 1000 mg/day versus placebo	6 weeks	100 patients	The incidence of side effects was low and similar in both groups. Three withdrawals were possibly drug-related: 2 in the placebo group (vertigo and drowsiness) and one in the diosmin group (nausea).
Geroulakos et al., 1994 [Ref. 12] Controlled studies of Daflon 500 mg in chronic venous insufficiency. Also reported as: Nicolaides et al., 1995 [Ref. 13] Objective evaluation of the pharmacological properties of Daflon 500 mg	Diosmin complex 1000 mg/day versus placebo	2 months	Review of data including 366 patients	Clinical side effects were rare and led to treatment withdrawal in only 3 patients.
Godeberge, 1994 [Ref. 15] Daflon 500 mg in the treatment of hemorrhoidal disease: a demonstrated efficacy in comparison with placebo.	Diosmin complex 1000 mg/day versus placebo	2 months	120 patients	Reported side effects were transient and of mild intensity: anxiety, shivering, oppressive feeling across the chest and epigastric pain.
Guilhou et al., 1997 [Ref. 20] Efficacy of Daflon 500 mg in venous leg ulcer healing: a double-blind, randomized, controlled versus placebo trial in 107 patients.	Diosmin complex 1000 mg/day versus placebo	2 months	107 patients	6 withdrawals from the study for reason other than ulcer healing: 2 in the diosmin group (1 phlebitis and 1 non-compliance) and 4 in the placebo group. Good tolerability of treatment.
Guillot et al., 1989 [Ref. 8] A long-term treatment with a venotropic drug. Results on efficacy and safety of Daflon 500 mg in chronic venous insufficiency.	Diosmin complex 1000 mg/day	1 year	215 patients	Side effects were essentially gastralgia and led to study discontinuation in only 4 cases. The safety of long-term administration was demonstrated. No abnormal changes in laboratory parameters were observed during the 12 months period.

Ho et al., 1995 [Ref. 18] Prospective randomized controlled trial of a micronized flavonoidic fraction to reduce bleeding after haemorrhoidectomy.	Diosmin complex (3000 mg for 3 days, then 1500 mg for 4 days) versus control group	7 days	228	No side effects were reported.
Jantet,2000, 2002 [Ref. 24, 25] Chronic venous insufficiency: worldwide results of the RELIEF study. Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids.	Diosmin complex 1000 mg/day	6 months	4527 patients	91 % of patients and 93 % of investigators judged the overall acceptability as good or excellent.
Laurent et al., 1988 [Ref. 5] Clinical evaluation of a venotropic drug in man. Example of Daflon 500 mg.	Diosmin complex 1000 mg/day versus placebo	2 months	200 patients (174 females and 26 males)	No allergic reaction, neither drug interaction was observed. Similar type and similar incidence of side effects were reported in the 2 groups. Only 1 patient in the diosmin group and 2 in the placebo group withdrew from the study.
Le Dévéhat et al., 1997 [Ref. 21] Evaluation of haemorheological and microcirculatory disturbances in chronic venous insufficiency: activity of Daflon 500 mg.	Diosmin complex 1000 mg/day versus placebo	2 months	88 patients	No clinically significant change in laboratory parameters.
Manuel y Keenoy et al., 1999 [Ref. 23] The effect of flavonoid treatment on the glycation and antioxidant status in Type 1 diabetic patients.	Diosmin complex 2000 mg/day versus placebo	3 months	28 patients	Treatment well tolerated. No adverse event reported.
Maruszynsky et al., 2002 [Ref. 4] A double blind, randomized study evaluating the influence of semisynthetic diosmin, and purified, micronized flavonoid fraction (diosmin and hesperidin), on symptoms of chronic venous insufficiency of lower limb	600 mg diosmin hemi-synthetic complex once a day vs. diosmin complex 1000 mg/day	4-weeks treatment	126 patients	Good tolerance. Recorded adverse events were mild and not numerous. Three patients withdrew prematurely due to side effect. Over the study, 6 adverse events were reported in 4 patients.
Meyer, 1994 [Ref. 2] Safety and security of Daflon 500 mg in venous insufficiency and in hemorrhoidal disease.	Diosmin Complex 1000 mg/day Non-micronized diosmin Placebo	From 6 weeks up to 1 year	Review of 12 trials including 3160 patients	Side effects in 10 % of patients in diosmin Complex group and 13.9 % in placebo group. Mainly GI side effects and autonomic disorders. Drop out rate for side effect was 1.1 % in the diosmin complex group and 3.2 % in the placebo group.

Roztocil et al., 2003 [Ref. 5] Efficacy of a 6-month treatment with Daflon 500 mg in patients with venous leg ulcers associated with chronic venous insufficiency.	Diosmin complex 1000 mg/day versus control group	6 months	150 patients	No treatment-related side effects. Acceptability considered excellent by 85 % of patients under diosmin.
Serfaty and Magneron, 1997 [Ref. 22] Premenstrual syndrome in France: epidemiology and therapeutic effectiveness of 1000 mg of micronized purified flavonoid fraction in 1473 gynecological patients	Diosmin complex 1000 mg/day	3 months	1724 women	Ten patients withdrew from the study because of a side effect. Acceptability was judged good or excellent by 98 % of patients.
Thanapongsathorn et al., 1992 [Ref. 9] Clinical trial of oral diosmin (Daflon) in the treatment of hemorrhoids.	Diosmin complex (6000 mg/day for 4 days and then 2000 mg/day for 10 days) versus placebo	14 days	100 patients	Two patients in the placebo group withdrew from the study due to clinical deterioration. No side effects of diosmin were reported.
Tsouderos, 1989 [Ref. 7] Are the phlebotonic properties shown in clinical pharmacology predictive of a therapeutic benefit in chronic venous insufficiency? Our experience with Daflon 500 mg.	Diosmin complex 1000 mg/day versus placebo	2 months	36 patients	No significant change in cardiac index, capillary filtration index, blood pressure, cardiac and respiratory rate.